REMARKS

Summary of Interview

The Examiner is thanked for the courtesy of the telephonic interviews with Applicants'representatives on May 17, 2005 and June 7, 2005. During those interviews the prior art and 35 USC 112, second paragraph rejections were discussed. The Examiner indicated during the June 6, 2005 interview that the amendments to claim 1 would be sufficient to overcome at least some of the 112, second paragraph rejections. While no resolution was reached, possible amendments to overcome the prior art were also discussed.

Pending claims

Claims 1, 5, 8-14, 21-24 and 75-82 are pending. Claims 1, 5, 8 and 21 have been amended to replace the term "said structures" with the term "said three dimensional conformations." Claims 1, 8 and 78 have also been amended to specify that the distance constraint information is applied to the candidate three-dimensional conformations to rank the conformations and that one or more conformations are selected based on the rankings. This amendment is supported by the specification, for example, at page 11, lines 20-29.

No new matter has been added.

The Rejections Under 35 USC 112, Second Paragraph

Claims 1, 5, 8-14, 21-24 and 75-82 are rejected under 35 USC 112, Second Paragraph. The rejections are addressed below.

The Examiner has rejected independent claims 1 and 8 as having insufficient antecedent basis for the limitation "said structures." Applicants have amended claims 1 and 8 to replace "said structures" with "said three-dimensional conformations," for which there is antecedent basis.

The Examiner has rejected independent claims 1, 8 and 78 for allegedly being vague and indefinite. Specifically, the Examiner contends that it is unclear from the claims what distance constraint information is being used to fulfill the best fit criteria.

Applicants believe that the distant constraint information is unambiguously specified for the reasons discussed in the December 15, 2003 and October 20, 2004 Amendments ("the previous Amendments"). Specifically, the physical and chemical

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properties of the crosslinking agent or the crosslink procedure as specified in the initial operations of the independent claims will unambiguously specify the distant constraint information to the person skilled in the art.

In addition, Applicants have amended claims 1, 8 and 78 to delete reference to selecting one or more structures that "best fit" the distance constraint information. The claims now recite that the three-dimensional conformations are ranked, and that conformations are selected based on the rankings. As explained in Applicants' specification, the distance constraint information may used to rank the candidate conformations. The rankings information may then used to select one or more conformations (page 11, lines 20-29). Applicants believe this amendment obviates this rejection.

Withdrawal of the rejections under 35 USC 112, second paragraph is respectfully requested.

The Rejections Under 35 USC 112, First Paragraph

Claims 77-82 are rejected under 35 USC 112, First Paragraph as allegedly containing subject matter not described in the specification in a way as to reasonably convey that the inventors have possession of the claimed invention at the time the application was filed. Each rejection is addressed below.

The Examiner states that the specific disclosure pointed to in the December 15, 2003 Amendment (page 29, lines 19-25) does not support the limitation "about 2-5 Angstroms" in claim 77. Applicants submit that this limitation is supported throughout the specification including at page 8, line 24 ("The invention herein can provide resolution of structures between about 2-5 Å").

Claim 78 specifies that the number of crosslinks in the protein is at least about 10% of the number of amino acid residues in the protein. The Examiner states that the specific disclosure (page 25) does not support the limitation "at least about 10% of the number of amino acid residues." Applicants submit that this limitation is supported throughout the specification. Specifically, Applicants repeatedly refer to about 10% of the number of amino acid residues as a guideline for the minimum number of cross-links to obtain a good prediction of the structure according to some embodiments (see, e.g., page 12, lines 23 and 24 "It has been found that a surprisingly small number of cross-links, typically about 10% of the number of amino acid residues, is adequate for purposes of the invention" and page 25, lines 1 and 2 "Even with few generated crosslinks (about 10% of the number of amino acid residues) it is

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possible to determine the fold-family for a sequence of unknown structure"). One of skill in the art would understand from these statements that about 10% of residues is a small number of crosslinks and, according to some embodiments, crosslinking at least about 10% of residues will result in the desired structural prediction. Applicants also specifically contemplate having a "large" number of crosslinks (see, e.g. page 9, lines 32-34 "MS technology permits the resolution of ... large numbers of crosslinks."). Thus, one of skill in the art would understand from the specification that Applicants were in possession of crosslinking about 10% or more of residues.

Thus, Applicants request that the Examiner withdraw these 35 USC 112, First Paragraph rejections of claims 77 and 78, as well as of claim 79-82, which were rejected for depending from a rejected claim.

The Rejections Under 35 USC 102 and 103

The Office maintained its rejection of claims 1, 5, 8-14, 21-23 and 75-77 based on the article by Lacroix et al. (1997) alone or in combination with the article by Mitra et al. (1979). Applicants acknowledge the withdrawal of the prior art rejections of claims 78-82. The rejections are traversed for the reasons set forth below.

As has been discussed in the previous Amendments, relevant limitations of the claims at issue include the following steps:

A. providing a set of candidate three-dimensional conformations for the protein's primary sequence; and

B. applying physical distance constraint information associated with the cross-linking for the identified cross-link fragments to the candidate three-dimensional conformations to rank said three-dimensional conformations and selecting one or more of said three-dimensional conformations based on the rankings.

The Examiner contends that Lacroix discloses step B, specifically pointing to the abstract where Lacroix disclosed "complementary information provided by chemical cross-linking and homology modeling studies was used to construct a three-dimensional model of the γ-B mono, in which module V interacts with the serine protease on the side opposite to both active site and the Arg446-Ile447 activation site." (Item 15 of the Office Action).

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As pointed out in the previous Amendments, the Lacroix's cross-linking produced intra-monomer cross-links (within a single γ-B) and inter-monomer cross-links (between the individual residues of the separate γ-B monomers in a $(\gamma\text{-B})_2$ dimer). The resulting cross-linked γ-B polypeptides were fragmented with a protease and subjected to mass spectrometry analyses. This analysis and subsequent sequencing of the fragments identified one intra-monomer cross-link between Lys426 of one CCP module and Asp688 of the serine protease B-domain. It also identified one inter-monomer cross-link between Gly280 of fragment γ and Glu493 of the B domain. The cross-link information was used in conjunction with homology modeling to position the domains of the γ-B monomer with respect to one another, thereby constructing a three-dimensional model of the γ-B monomer, in which a CCP module interacts with a serine protease on a side opposite to both the active site and the Arg446-Ile447 activation site.

Step B requires selecting one or more candidate conformations for the protein under consideration by applying distance constraint information (obtained from the cross-link data) to the candidate conformations. In contrast, Lacroix et al. apply cross-link data to whole domains (of fixed conformation) to position those domains with respect to one another.

During the May 17, 2005 telephonic interview, the Examiner further pointed to the paragraph beginning at the bottom of the first column of page 6280, wherein Lacroix discusses the three-dimensional model of the assembly of the whole domains (the CCP modules IV and V, the intermediary segment and the serine protease domain) of the γ-B monomer constructed from the information from the cross-linking and homology studies and available structural information. Specifically, Lacroix describes using cross-linking information (the cross-link between Lys426 of one CCP module and Asp688 of the serine protease B-domain) and available structural information (the Cys434 – Cys560 disulfide bond connecting the intermediary segment to the protease domain) to position the Clr domains or modules with respect to one another (page 6280, 2nd col., lines 14-20). Lacroix does not disclose selecting one or more candidate conformations for the protein under consideration by applying distant constraint information.

With regard to Step A, it appears that the Examiner is taking the position that Lacroix meets this limitation by providing models of the γ-B domains (Item 18 of the

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Office Action, in which the Examiner equates "primary sequence" with the Protein Data Bank coordinates of the modules). Under this analysis, the three-dimensional conformations are the different γ-B modules of Lacroix. Following this analysis, the crosslinking information would be used to select one of these modules if Lacroix had Step B. However, the only time crosslinking information is used in Lacroix is in assembling the different modules together to construct the γ-B monomer. Nowhere does Lacroix teach or suggest selecting one of these modules as required by Step B.

Even if one equated the γ-B monomer with the three-dimensional conformation in the instant claims, Lacroix does not teach or suggest providing multiple candidate conformations of the γ-B monomer and using distance constraint information to rank and select one of the conformations as the claims require.

Thus, as discussed in the previous Amendments, Lacroix does not provide a set of candidate conformations and apply physical distance constraint information to choose a three-dimensional conformation from among these multiple candidate conformations. Additionally, applicants have addressed a possible concern of the Examiner raised in paragraph 16 of the Office Action:

> 16. Applicant argues that Lacroix et al. does not apply physical distance constrain information for the identified cross-link fragments to choose a three-dimensional structure from among these multiple structures. Applicants argument is not persuasive because the argued limitation is not present in the instant claims.

To address this, Applicants have amended the independent claims to explicitly state that a three dimensional conformation is chosen from among the multiple candidate conformations. Applicants believe that this amendment clearly distinguishes the instant claims from Lacroix for the reasons stated above and given in the previous Amendments.

In addition, as discussed above Applicants have amended the claims to specify that the distance constraint information is applied to the candidate conformations to rank the conformations and selecting one or more conformations based on the rankings. Nowhere does Lacroix disclose or suggest ranking candidate conformations.

Mitra et al. does not suggest the claimed features that are lacking in Lacroix et al. (e.g., neither Lacroix et al. or Mitra et al. suggest "applying physical distance constraint information associated with cross-linking for the identified cross-link

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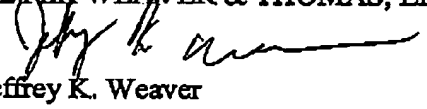
fragments to the candidate three-dimensional conformations to rank said three-dimensional conformations and selecting one or more of said three-dimensional conformation based on the rankings").

Thus, Applicants submit that independent claims 1, 8 and 78 are patentable over the prior art. As all independent claims are patentable over the cited art, the dependent claims are patentable as well. Therefore withdrawal of the rejections of claims 1-3, 5, 8-14, 21-24 and 75-77 is respectfully requested.

Conclusion

Applicants respectfully submit that all pending claims are allowable and respectfully requests a Notice of Allowance for this application from the Examiner. If the Examiner wishes to telephone the applicants representative concerning any matter pertaining to this case, the Examiner is cordially invited to do so at the telephone number set out below. The Commissioner is hereby authorized to charge any additional fees to Deposit Account 500388 (Order No. UCSFP001).

Respectfully submitted,
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